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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,000	06/09/2005	Pieter Jan Arnoldus Maria Plomp	4662-25	8720

23117 7590 03/01/2011
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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
03/01/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,000	PLOMP ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,22-26,28,29 and 32-40* is/are pending in the application.

4a) Of the above claim(s) *1-9,26,28,29 and 35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-25,32 and 40* is/are rejected.

7)☒ Claim(s) *33 and 34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *alignment*.

DETAILED ACTION

Status of the Application

Claims 1-9, 22-26, 28-29, 32-40 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/28/2011 has been entered.

Applicant's amendment of claims 33-34 as submitted in a communication filed on 1/28/2011 is acknowledged.

Claims 1-9, 26, 28-29, 35-39 remain withdrawn from consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 22-25, 32-34 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

1. Claim 33 is objected to due to the recitation of "an isolated....with an amino acid sequence comprising..". To be consistent with commonly used claim language, it is suggested the term be amended to recite "an isolated...comprising the amino acid sequence of SEQ ID NO: 3". Appropriate correction is required.

2. Claim 34 is objected to due to the recitation of "an isolated....with an amino acid sequence at least.....". To be consistent with commonly used claim language, it is suggested the term be amended to recite "an isolated...comprising an amino acid sequence which is at least 95% identical to SEQ ID NO: 3". Appropriate correction is required.

3. Claims 40 is objected to due to the recitation of "hybridizes ..conditions to the complement of SEQ ID NO: 1 or 2...". As known in the art, (a) nucleotide sequences are merely graphical representations of the order in which nucleotides are arranged in a nucleic acid molecule, and (b) hybridization occurs only among nucleic acid molecules. Therefore, for clarity and consistency, it is suggested the term be amended to recite "hybridizes....to the....of the polynucleotide of SEQ ID NO: 1 or 2...". Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

4. The text of those sections of Title 35, U.S. Code not included in this rejection can be found in a prior Office action.

5. Claim 23 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. This rejection as it relates to claim 23 has been discussed at length in the previous Office action mailed on 4/1/2009, the Final action of 12/28/2009 and the Advisory action of 10/25/2010. The rejection of claim 23 is maintained for the reasons of record and those set forth below.

7. It is reiterated herein that neither the specification nor the art provides the structural characteristics required in any structural homolog of the polypeptide of SEQ ID NO: 3 having 90% sequence identity to SEQ ID NO: 3 which would allow one of skill in the art to recognize whether such homolog is an A. niger asparaginase. As previously indicated, there is no teaching or suggestion in the art or the specification indicating that all A. niger asparaginases would have 90% or more sequence identity to SEQ ID NO: 3, or that all A. niger asparaginases would comprise SEQ ID NO: 3. In fact, the teachings of Louboudy S. (Egyptian Journal of Biotechnology 4:110-123, 1998; cited in previous Office

actions) are further evidence that there is structural/functional variability among asparaginases from A. niger since the asparaginase of Louboudy appears to have a different pH optimum from that of the polypeptide of SEQ ID NO: 3, which would strongly suggest that the asparaginase of Louboudy has a different structure than that of the polypeptide of SEQ ID NO: 3 since structure determines function. In view of the fact that the identifying structural features of A. niger asparaginases have not been disclosed either in the specification nor the art, one cannot reasonably conclude that the identifying characteristics of the recited genus of A. niger asparaginases have been adequately described in the instant application.

8. Claims 22-25, 32, 40 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the asparaginase of SEQ ID NO: 3, does not reasonably provide enablement for (a) an asparaginase which is at least 90% sequence identical to the polypeptide of SEQ ID NO: 3, (b) any asparaginase encoded by a polynucleotide which hybridizes under the conditions recited in claim 24, or (c) an asparaginase comprising an enzymatically active fragment of (b). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or ;use the invention commensurate in scope with these claims.

9. This rejection as it relates to claims 22-25, 32, 40 has been discussed at length in the previous Office action mailed on 4/1/2009, the Final action of 12/28/2009 and the Advisory action of 10/25/2010. The rejection of these claims is maintained for the reasons of record and those set forth below.

10. While the molecular biology techniques required to make the claimed polypeptides are known in the art, and enzymatic assays are available to test whether a variant has asparaginase activity, the issue with regard to the instant rejection is how much experimentation would be required to enable the entire scope of the claims. Using the calculations provided by the Examiner in a previous Office action with regard to 80% sequence identity homologs of the polypeptide of SEQ ID NO: 3, one could determine that the total number of 90% sequence identity homologs of the polypeptide of SEQ ID NO: 3 which are the

result of amino acid substitutions is $378!x19^{38}/(378-38)!/38!$ (SEQ ID NO:3 has 378 amino acids; 38 amino acids = 0.1x378) or $9.6x10^{100}$ variants. Since nothing is known about the structural features required among all these variants to have asparaginase activity, or the structural features which are characteristic of A. niger asparaginases, one of skill in the art would have to test an infinite number of proteins to determine which ones have activity and which ones are naturally found in A. niger.

With regard to the polypeptides encoded by the nucleic acids that hybridize to the polynucleotides of SEQ ID NO: 1 or 2 under the recited conditions, it is noted that these polypeptides can have little structural homology with the polypeptide of SEQ ID NO: 3. First, a nucleic acid which hybridizes under the conditions recited to a complement of the polynucleotide of SEQ ID NO: 1 or 2 is a nucleic acid that does not have to hybridize to the full-length complement of the polynucleotide of SEQ ID NO: 1 or 2 since, in the absence of a limitation regarding length, a complement can be a fragment of the full-length complement of the polynucleotide of SEQ ID NO: 1 or 2 that hybridizes under the recited conditions. Thus, the nucleic acid encoding the claimed enzyme can be a nucleic acid which hybridizes to a fragment of any size of the full-length complement of SEQ ID NO: 1 or 2 under the conditions recited. Second, even if one were to interpret the term "complement" as "full-length complement", a calculation of the Tm of the polynucleotide recited in claim 24 shows that under the hybridization conditions recited, the recited nucleic acid would have 66.2% sequence identity with the polynucleotide of SEQ ID NO: 1 or 2. Using the well known equation of Meinkoth and Wahl (Current Protocols in Molecular Biology, Hybridization Analysis of DNA Blots, pages 2.10.8-2.10.11, 1993), $Tm = 81.5\ ^{\circ}C + 16.6x\log_{10}[Na+] + 0.41x(\%GC) - .61x(\%form) - 500/L$, the corresponding Tm for the polynucleotide recited is approximately 101.8 °C assuming a G+C content of 50% and neglecting the term 500/L (L=length of polynucleotide) (101.8 °C = $81.5 + 16.6x\log_{10}[3.9x5/20] + 0.41x(\%50) - .61(\%form = 0)$; for 20xSSC the molar concentration of Na+ is 3.9). As known in the art, Tm is reduced by approximately 1 °C for each 1% mismatching, therefore under the conditions recited (5xSSC and 68 °C), this is equivalent to approximately 33.8% mismatching

(33.8% = 101.8°C – 68°C). This level of mismatching amounts to 384 nucleotides for the polynucleotide of SEQ ID NO: 2 which can be modified (384 = 0.338x1137) within SEQ ID NO: 2 (1090 nucleotides can be modified within SEQ ID NO: 1; 1090 = 0.338x3223). Since a great number of these mismatches can each affect one codon, a protein encoded by a variant of the polynucleotide of SEQ ID NO: 1 or 2 that hybridizes under the conditions recited can essentially have little structural homology with the polypeptide of SEQ ID NO: 3.

It is also noted that under the wash conditions recited, Tm according to the equation of Meinkoth and Wahl would be reduced to 78.61 C (0.2xSSC and 25 C). The % mismatching under these conditions is 53.61% (= 78.61 C- 25 C; at least 46.39% (100% - 53.61%) sequence identical to the polynucleotides of SEQ ID NO: 1 or 2). While the hybridization conditions result in approximately 33.8% mismatching (at least 66.2% sequence identical to the polynucleotides of SEQ ID NO: 1 or 2; see calculations above), there is the potential for obtaining nucleic acids which have higher % mismatching if the wash conditions are less stringent than the hybridization conditions, which is the case herein.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. Therefore, testing the essentially infinite number of polypeptides which are encoded by the genus of nucleic acids that hybridize under the conditions recited to the polynucleotides of SEQ ID NO: 1 or 2, or the essentially infinite number of 90% sequence identity homologs of the polypeptide of SEQ ID NO: 3 and determine which ones have asparaginase activity would constitute undue experimentation.

Claim Rejections - 35 USC § 102

11. The text of those sections of Title 35, U.S. Code not included in this rejection can be found in a prior Office action.

12. Claims 24, 32 and 40 remain rejected under 35 U.S.C. 102(b) as being anticipated by Minton et al. (PIR accession number A26064, 1999). This rejection has been discussed at length in previous Office actions. It is maintained for the reasons of record and those set forth below.

13. Claims 24, 32 and 40 are directed in part to an asparaginase which is encoded by a nucleic acid that hybridizes under the conditions recited in claim 24 to the complement of the polynucleotide of SEQ ID NO: 2.

14. As previously indicated, the asparaginase of Minton et al. is 43.1% sequence identical to the polypeptide of SEQ ID NO: 3. See alignment provided with the Non Final action of 4/1/2009. This asparaginase is encoded by a nucleic acid which is 68% sequence identical to the polynucleotide of SEQ ID NO: 2 (68% = 771 matches x 100/1137; SEQ ID NO: 2 = 1137 nucleotides). See attached alignment and nucleotide sequence encoding the protein of Minton et al. (1044 nucleotides) below:

atg gaa aga tgg ttt aaa tct ctg ttt gtt ctt gtt tta ttt ttt gtt ttt acg gcc tcg gcg gcc gac aag ctg ccg aac ata gtc att ctc gca acg ggt ggt acc atc gcg ggc tcc gct gcc acc gga acc cag acg acc ggc tac aag gcc gga gca ctc ggg gtc gat acc ctc atc aat gcg gtg cca gag gtg aag aaa ctg gcc aat gtt aag ggc gag cag ttc tcc aac atg gcc agc gag aac atg acc ggt gac gtg gtg ctt aag ctg tcc cag cgg gtg aac gag ctg cta gca cgg gac gat gtg gac ggt gtt gtc atc acc cac ggc acc gac acc gtg gag gag tct gcc tac ttc ctg cac ctc act gtc aaa agt gac aag cca gtt gtc ttt gtg gct gcc atg cgc cca gcc acg gcc atc tca gct gac ggg ccc atg aat ctg ctc gaa gcc gtg cgg gtg gct ggc gac aag cag tcg cgc ggt cgc ggt gtc atg gtg gtc ctc aac gat cgc att ggc tcg gcc cgc tat atc acc aag acc aat gcc tcc act ctg gac acc ttc aag gcc aat gag gag ggc tac ctt ggc gtg atc atc ggc aac cgc att tac tac caa aac cgt atc gac aag ctg cat acc act cgg tcg gtc ttt gac gtc cgc ggc ctg act tcg ctc ccc aaa gtg gac att ctg tat ggt tat cag gac gac ccc gaa tac ctc tac gac gcc gcc atc cag cat ggt gtc aag gga att gtg tat gcc ggg atg ggt gct gga tcc gtc tca gtt cgt ggt att gcc ggc atg cgt aag gct atg gag aaa ggg gtc gtt gtc ata cgg agt acg cgc aca ggc aat ggg ata gtg cca ccc gac gaa gag ctc ccc ggc ctc gtc agt gac tcc tca aac ccg gcg cat gcc cgc att ctg ttg atg ttg gcg cta act cgg aca agt gat cct aaa gta atc caa gag tat ttt cat acg tat

As explained before, a nucleic acid which is 66.2% sequence identical to the polynucleotide of SEQ ID NO: 1 or 2 (% identity that is equivalent to the hybridization conditions recited in the claims) can potentially encode a protein having little structural homology to the polypeptide of SEQ ID NO: 3 since this level of identity amounts to up to 384 mismatches in the polynucleotide of SEQ ID NO: 1 or 2. See

above for calculations. If most of these mismatches affect a codon, one could have a situation where the protein encoded by the 66.2% nucleic acid variant would have very little sequence identity with the polypeptide of SEQ ID NO: 3, which is 378 amino acids long. In the instant case, the nucleic acid indicated above is a nucleic acid which encodes the asparaginase of Minton et al. and has a sequence identity with respect to the polynucleotide of SEQ ID NO: 2 which is higher than that which corresponds to the sequence identity equivalent to the hybridization conditions recited (66.2%). If we were to consider only the wash conditions, the nucleic acid indicated above would also have a sequence identity with respect to the polynucleotide of SEQ ID NO: 2 which is higher than that which corresponds to the sequence identity equivalent to the wash conditions recited (46.39%). See above for calculations regarding sequence identities that correspond to the conditions recited. Since the asparaginase of Minton et al. is encoded by a nucleic acid that would hybridize under any of the conditions recited, the asparaginase of Minton et al. anticipates the instant claims as written.

Allowable Subject Matter

15. The subject matter of claims 33-34 appear to be allowable over the prior art of record.

Conclusion

16. No claim is in condition for allowance.

17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (571) 272-0956. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
February 28, 2011